REMARKS

Favorable reconsideration is respectfully solicited in view of the following remarks.

Initially, Applicant wishes to express its sincere thanks for the courtesy and cooperation provided to its undersigned representative by Examiner Timothy Thomas and Supervisory Examiner Ardin Marschel during the personal interview held on November 20, 2008. The following is a summary of the items discussed during the interview.

Claims 19, 39, 40, 41, 61, 62 and 63 have been amended to require that the aqueous liquid preparation is in the form of an eye drop. Claims 30, 35, 52 and 57 have accordingly been cancelled.

Claim 41 has been amended to delete "at least" and to change "comprising" to – is –.

Claim 63 has been amended to change "comprising" to – is – and to add --and water --.

Turning to the Official Action, Applicants acknowledge with thanks the Examiner's indication that numerous former grounds of rejection have been withdrawn in view of Applicants' last response.

On page 3, claims 19-29, 31-34, 36-38, 41-51, 53-56, 58-60 and 63 are rejected under 35 U.S.C. 103 as obvious over Gamache et al. (WO 01/15677) in view of ISTA or Nolan et al. This ground of rejection is respectfully traversed as applied to the amended claims.

Claims 19, 39, 40, 41, 61, 62 and 63 have been amended to require that the aqueous liquid preparation is in the form of an eye drop according to claims 30, 35, 52 and 57. None of claims 30, 35, 52 or 57 were encompassed by the rejection.

Accordingly this ground of rejection is deemed to be overcome.

Furthermore, Applicants take the opportunity to provide additional remarks for the Examiner's consideration against a potential 103 rejection based upon a different combination of references.

The subject matter of the claimed invention is directed to an eye drop having a specific combination of 2-amino-3-(4- bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a

polyethylene glycol fatty acid ester.

On the other hand, Gamache et al. do not disclose or suggest this specific combination. The cited reference is directed to compositions comprising of 5-HT_{1D} and/or HT_{1B} agonists. The cited reference states that these agonists may be combined with an extensive list of other pharmaceutical agents, i.e. (1) anti-microbial agent, (2) anti-inflammatory agents or (3) anti-allergy agent (please see page 6, lines 1-3 of Gamache). Gamache et al. only describes "bromfenac" as one of many examples of anti-inflammatory agents enumerated on page 12, lines 11-24. Gamache et al. does not concretely describe nor suggest the claimed preparation containing bromfenac.

Further, tyloxapol (0.05% w/v) is only mentioned as being added to an 1B/1D agonist (0.1-1.0% w/v) and moxifloxacin (0.3% w/v) in Example 4 (an Example of an otic/nasal suspension). There is no explanation about tyloxapol in the description of Gamache et al. or why it is included. Moreover in this Example, moxifloxacin is incorporated as a well-known antibacterial agent but is not an anti-inflammatory agent like bromfenac. Thus it is unclear from Gamache et al. why tyloxapol is added to the otic/nasal suspension containing 1B/1D agonist and moxifloxacin.

"Tyloxapol" described in Example 4 is just a single word description and does not give any clues and hints to the present invention. Therefore, the word "tyloxapol" described only in Example 4 does not destroy the novelty of the present invention.

Further, Gamache et al. is silent about an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester component according to the claimed eye drop.

Thus the disclosure of Gamache et al. would suggest to the skilled artisan thousands of possible combinations of ingredients to include with an IB/ID agonist. Such disclosure does not lead the artisan to the claimed specific combination nor does such disclosure render the claimed combination obvious. The prior art must motivate one skilled in the art to make the claimed combination. There is no teachings or suggestion in Gamache of selecting bromfenac in combination with an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

Furthermore, Gamache et al. is directed to compositions for relieving otic pain (abstract) by apply the compositions to the ear or nasally (page 10, lines 6-9 and Example 4). There is no teaching or motivation to make the claimed eye drop.

Regarding claims 41-51, 53-56 and 58-60, the claims are directed to an eye drop which consists essentially of the recited specific combination of ingredients. The claim recites the transitional phrase "consisting essentially of" means that the claim is open to include the specified ingredients and additional ingredients that do not materially affect the basic and novel characteristics of the claimed invention. See M.P.E.P. 2111.03.

It is respectfully submitted that the principal IB/ID agonist of the Gamache composition would affect the basic novel properties of the claimed preparation.

One skilled in the art would not have been motivated to modify the Gamache et al. composition in view of ISTA and Nolan, to arrive at the claimed eye drop. The primary object of Gamache et al. is to make a composition containing an IB/ID agonist. The artisan would not have been motivated by the reference to make a composition lacking the IB/ID agonist. An IB/ID agonist is excluded from claims 41-51, 53-56 and 58-60 by the "consisting essentially of" transitional phrase.

Regarding claim 63, the claim is limited to an eye drop which "consists of" the recited bromfenac, recited an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester, and water. Such claim explicitly excludes other ingredients, such as an IB/ID agonist.

For the foregoing reasons, Applicant submits that the present invention is unobvious from Gamache et al. and ISTA or Nolan to those skilled in the art.

Claims 41-60 and 63 are rejected under 35 USC 112, second paragraph, as being indefinite for the reasons set forth on pages 6-7 of the Action.

Based upon the Examiner's remarks during the personal interview, it is believed that this ground of rejection is overcome by the foregoing amendments.

Claims 19-38, 41-60 and 63 are rejected under 35 USC 103 as being unpatentable over Hellberg et al. and Nolan et al. This ground of rejection is respectfully traversed as applied to the amended claims.

The Examiner asserts that it would have been obvious to substitute the compounds having anti-inflammatory and anti-oxidant activity used in the ophthalmic compositions of Hellberg et al. with bromfenac used in the dermal applications disclosed in Nolan et al. Applicants respectfully disagree.

The intended purpose of the invention disclosed in Hellberg et al. is to provide "[c]ompounds having anti-inflammatory ***and*** antioxidant activity." See Hellberg et al., Abstract (emphasis added); see also Hellberg at column 2, lines 13-18 ("***The present invention provides*** new compounds having potent anti-inflammatory ***and*** anti-oxidant activity.") (emphasis added). Indeed, Hellberg et al. explicitly state that the principle of operation of the anti-inflammatory and antixodixant compounds is to provide a two-pronged therapeutic approach not previously available in the art:

> The compounds of the present invention are capable of protecting against cellular damage by a wide range of insults. Since the compounds provide this protection by decreasing free radical or oxidative damage, reducing cyclooxygenase or lipoxygenase mediated inflammation, and improving site delivery, this therapy represents an improved two-pronged approach to cytoprotection.

See Hellberg et al. at Column 2, lines 57-63. Therefore, the intended purpose of the invention disclosed in Hellberg et al. is to provide compounds with not only anti-inflammatory activity, but also anti-oxidant activity for improved therapeutic functionality:

> The compounds also include an anti-oxidant component. As oxidative stress has been implicated in inflammatory responses, the presence of an anti-oxidant will further help treat the target tissue.
>
> The compounds of the present invention also exhibit properties present only in the combined molecule, ***not in the individual components***. One such property is the inhibitory efficacy against 5-lipoxygenase, an enzyme known to be involved in inflammation.

See Hellberg et al. at Column 2, lines 38-45 (emphasis added).

The USPTO has made clear that "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." See MPEP section 2143.01 V, citing *In re*

Gordon, 733 F.2d 900 (Fed. Cir. 1984). Additionally, section 2143.01 VI of the MPEP plainly states: "The proposed modification cannot change the principle of operation of a reference. If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." See also *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

Here, the Examiner asserts that it would have been obvious to substitute the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac as disclosed in Nolan et al. because of "the art recognized equivalent activity of bromfenac as an anti-inflammatory agent in topical usage." See Official Action date July 18, 2008 at page 9. But as indicated in the Official Action and in Hellberg et al., bromfenac is an anti-inflammatory and not an antioxidant. The proposed substitution of the dual action anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac would render the Hellberg et al. invention unsatisfactory for its intended purpose of providing "compounds having potent anti-inflammatory and anti-oxidant activity." The proposed substitution would result in a bromfenac composition having only anti-inflammatory activity. This proposed modification would radically change the principle of operation of Hellberg et al. from "an improved two-pronged approach to cytoprotection" to a mere one-pronged approach based on anti-inflammatory action alone.

Therefore, because the proposed substitution of the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. with bromfenac as disclosed in Nolan et al. would render the Hellberg et al. invention unsatisfactory for its intended purpose and radically change the principle of operation of Hellberg et al., Applicants respectfully submit a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

In addition to the argument that the proposed modification changes the principle operation and intended purpose of Hellberg et al., Applicants submit that Hellberg et al. explicitly teach away from the use of a compound, such as bromfenac, having only anti-inflammatory activity. Hellberg et al. clearly recite deficiencies in the use of non-steroidal anti-inflammatory agents such as bromfenac:

> Non-steroidal anti-inflammatory agents (NSAIA) have been used for the treatment of inflammatory disorders. The following references may be referred to for further background concerning this use of NSAIAs:
>
> Ophthalmoscope, volume 8, page 257 (1910);
>
> FASEB Journal, volume 1, page 89 (1987); and
>
> Inflammation and Mechanisms and Actions of Traditional Drugs, vol. I Anti-inflammatory and Anti-rheumatic drugs. Boca Raton, Fla., CRC Press, (1985).
>
> However, ***there are some problems associated with NSAIA treatment including delivery to the appropriate site of action and side effects*** (Goodman and Gilman's The Pharmacological Basis of Therapeutics, pages 638-669, Pergman Press, NY (1990)).

See Hellberg et al. at Column 1, lines 28-37 (emphasis added).

According to the USTPO guidelines, "[i]t is improper to combine references where the references teach away from their combination." See MPEP § 2145, citing *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); see also *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed.Cir. 2001) ("It is well-established that references which "teach away cannot serve to create a prima facie case of obviousness.") (citations omitted).

Here, Hellberg et al. plainly state that NSAIA treatment is associated with "problems" such as "side effects" and "delivery to the appropriate site of action." In light of this teaching away from the use of a non-steroidal anti-inflammatory agent (NSAIA), one skilled in the art would not substitute bromfenac, a known NSAIA, for the anti-inflammatory and anti-oxidant compounds disclosed in Hellberg et al. Therefore, because Hellberg et al. teach away from the use of bromfenac, Applicants respectfully submit a prima facie case of obviousness cannot be based on the combination of Hellberg et al. and Nolan et al.

For the reasons detailed above, Applicants respectfully request withdrawal of the rejection of claims 19-38, 41-60 and 63 under 35 USC 103 as being unpatentable over Hellberg et al. and Nolan et al.

Lastly, claims 19-38 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-43 of copending

application Serial No. 11/755,662.

The Examiner is respectfully requested to hold this provisional ground of rejection in abeyance until a later date. Upon overcoming all other grounds of rejection, it is respectfully submitted that this provisional ground of rejection should be withdrawn and the application passed on to allowance.

In summary, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly such allowance is solicited.

Respectfully submitted,

Shirou SAWA et al.

By: 

Warren M. Cheek
Registration No. 33,367
Attorney for Applicants

WMC/dlk
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
January 15, 2009